Development of a Percutaneous Connector System

Quarterly Progress Report Number 5

August 1, 1998

Subcontractor

Huntington Medical Research Institutes

Neurological Research Laboratory

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THIS QPR IS BEING SENT TO YOU BEFORE IT HAS BEEN REVIEWED BY THE STAFF OF THE NEURAL PROSTHESIS PROGRAM.

Introduction

The objective of this project is to develop a percutaneous connector with a high contact density. In this quarter of the contract, we present the results from two animals: TC-24 and TC-28. Devices are currently under development that are expected to exhibit good biocompatibility and optimal base pedestal osseointegration, and with adequate soft tissue attachment to the lower stage and base pedestal.

Electrical leak test was performed on TC-28, 38 days after implantation and 24 days after the start of bias test. Histologic evaluations of the metal-bone interface and surrounding soft tissues were performed using light microscopy. In both animals, we found good osseointegration in spite of the fact that one animal presented a significant soft tissue infection surrounding the base pedestal.

Methods

Percutaneous Connector Design. The percutaneous connector has been described in detail in previous QPR's. Briefly, the percutaneous connector consists of a base pedestal composed of titanium metal. The underside of the pedestal is composed of sintered titanium beads, and the sides have circumferential milled grooves, ca. 100 μm deep and 125 μm wide. The beads and grooves have been designed to facilitate the attachment of bone, skin and muscle tissues to the connector. The lower (percutaneous) stage contains the pin grid array, pin-wire bonds, silicone and epoxy potting surrounded by a titanium ring with circumferential grooves approximately 20 μm deep and 40 μm wide. The upper connector stage, i.e., the mating system, resides above the skin line. The configuration of the upper connector stage was slightly different in each of the three cats.

Surgical Procedures. A rainbow-type incision measuring approximately 4 cm was made on the right parietal hemisphere. The skin and muscles were retracted from the left hemisphere. A mark was made 16 mm distal to the sagittal fissure and 9 mm from the midline at which point a central hole was drilled to accept the tip of the major drill, which was used to shape the skull to confirm to the bottom of the pedestal. The drill worked very well, and the pedestals fit the convexity satisfactorily. The retaining screws were inserted into the skull using a torque wrench. The pedestals appeared to be firmly attached to the skull. A disc of skin was removed with a skin punch, and its aperture in the skin was fitted snugly over the connector. The lower stage and protective Teflon caps were added to the base pedestal in TC-24. The dummy upper stage was removed three days later because the skin rode over the implant. After removal of the upper stages of the connector, the skin defect was debrided and the muscles were sutured over the pedestal, and to the outer surface of the intact muscles on the right side. The galea was closed as the second layer, bacitracin was added, and the skin wound was closed.

Vascular Perfusion, Embedding and Sectioning.

Twenty-eight weeks (TC-24), or seven weeks (TC-28) after surgical placement of the connectors, anesthetized animals were perfused with PBS for blood removal followed by ½ Karnovsky's Fixative in 0.1 M Schultz's Phosphate Buffer at pH 7.3. The head of the animals were placed in the above-mentioned fixative and remained in a cold room for 1-3 days prior to removal of the connectors. Each connector and associated skin, muscle and bone was removed with a Lipshaw Bone Saw as a single tissue block (connector blocks). The connector blocks were immersed into fresh fixative for several additional days. All connector blocks were embedded in glycol methacrylate and 20-40 μm sections were cut with a Beuhler Saw. Unpolished sections were mounted on glass slides with a rapid bonding adhesive and were stained with toluidine blue for light microscopy.

Results

Autopsy Results. Gross necroscopic evaluation of TC-24 revealed that the skin was completely healed over the base pedestal. In TC-28, there was an open wound partially exposing the base pedestal. There was dried, encrusted material at the edges of the skin. In both animals, a 0.5 mm circle of skin and muscle tissues remained intact surrounding the connector.

Histology. In animal TC-24, the skin, subcutaneous tissue and muscle completely healed over the base pedestal. No infection was associated with either the sides of the connector or within the base pedestal/bone interface. In this animal, there was good soft tissue attachment to the enlarged grooves of the base connector. (Fig. 1). In TC-28, however, there was less attachment of the reticular layer of the dermis and subcutaneous skin layers to the sides of base pedestal stages of the connector (Figs. 2-4). Inflammatory cells were associated with purulent material near the edges of the connector and within the recesses of the bone screws (Figs. 5, 6). Cells types within the inflammatory lesions included neutrophils, mononuclear cells and phagocytes (Fig.

4). An occasional inflammatory cell was seen under the edges of the base pedestal. The width of the pedestal base-bone interface was measured in these histologic sections using an ocular lens scale on an Olympus Light Microscope. Osseointegration was identified as osteoid tissue directly attached to the opaque titanium metal. Any evidence of blue stained, fibrotic subcutaneous connective tissue within the bone-metal interface was interpreted as the absence of osseointegration. The average amount of osseointegration for both animals was calculated as 81% of the cross-section area of the base pedestal, based on three representative regions (edges and the central portions of the connector) Fig. 7). In both animals, there was excellent osseointegration of the titanium screws into the skull (Figs. 5, 8).

ANIMAL #	LOCATION OF INFLAMMATION	AVERAGE OSSEOINTEGRATION
TC-24	None	88%
TC-28	Pedestal sides within the dermis and subcutaneous tissue extending to the periphery of the pedestal-bone interface. Within the recesses of connector bone screws	81.3%

TABLE I

Discussion and Future Studies

The most important observations made in this quarter was the good osseointegration observed in the base pedestals in two cats.

1) Skin Attachment to the Metal Connector. Similar to previous experiments, our results suggest that the dermis and subcutaneous portions of the skin appeared to attach better to the deeply grooved titanium surfaces. If infection is present, however, soft tissue attachment may be reduced.

2) Osseointegration and Possible Affects of Infection. We speculate that chronic skin infection may prevent adequate osseointegration. As we pointed out in our previous QPR, if inflammatory cells and/or microbial pathogens can release toxic substances, than osteoblasts (and connective tissue) may be affected. Previous experiments appeared to have supported this premise but, some animals demonstrated soft tissue infection and adequate osseointegration. Although these data remain equivocal at present, the results from two animals presented here also suggest that infection may not significantly interfere with osseointegration. This question is of critical important because we wish to establish precisely how much osseointegration will be adequate for human application. We will pay close attention to this problem in future animals.

In future animals, we will continue light microscopic studies to determine if the skin and subcutaneous tissues attach differently to grooved and machined metal surfaces. In one study, one half of the surface of its side will be coated with sintered titanium beads, while the other half will be uncoated and will have a smoother, machined surface. The application of substances that may promote soft tissue attachment and reduce infection (eg. laminin-5, homologous IgG) are also being explored. Further, immunocytochemical studies to identify leukocyte subsets are also being conducted in the cat model. We would like to know what inflammatory cell subsets within the skin infection may play a role in altering the metal-soft tissue and metal-bone interfaces.

Fig. 1. TC-24. The subcutaneous tissue and skeletal muscle well attached to the deep groves on the sides of the base pedestal (*). Bar = 500 μm.

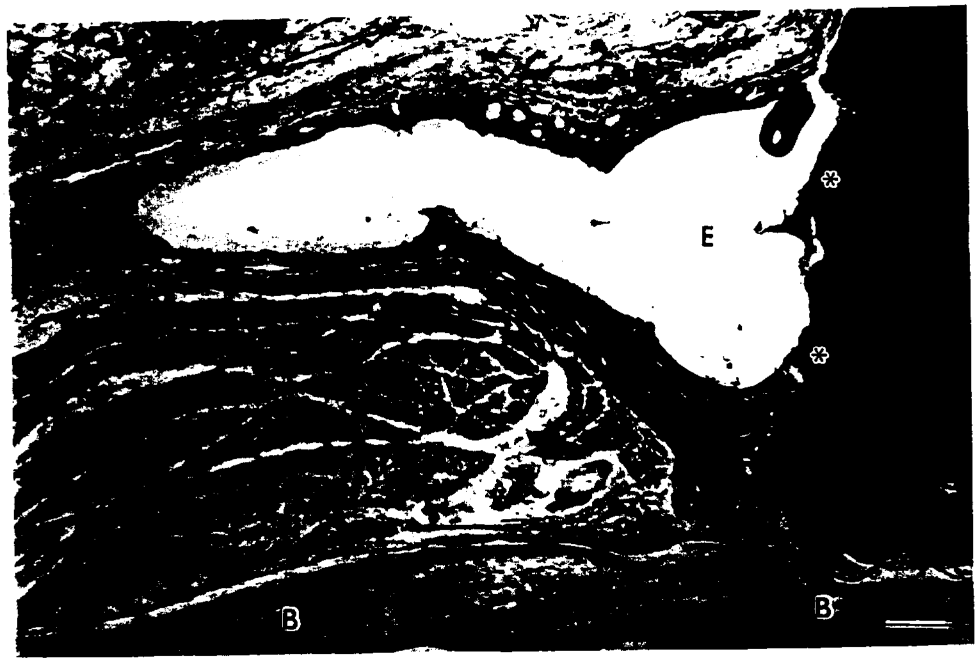

Fig. 2. TC-28. Infection of the soft tissue often reduces the soft tissue attachment to the grooved sides of the base pedestal (*). A large empty space (E) is also shown. The skull bone (B) is shown at the bottom of the micrograph. Bar = 200 μm.

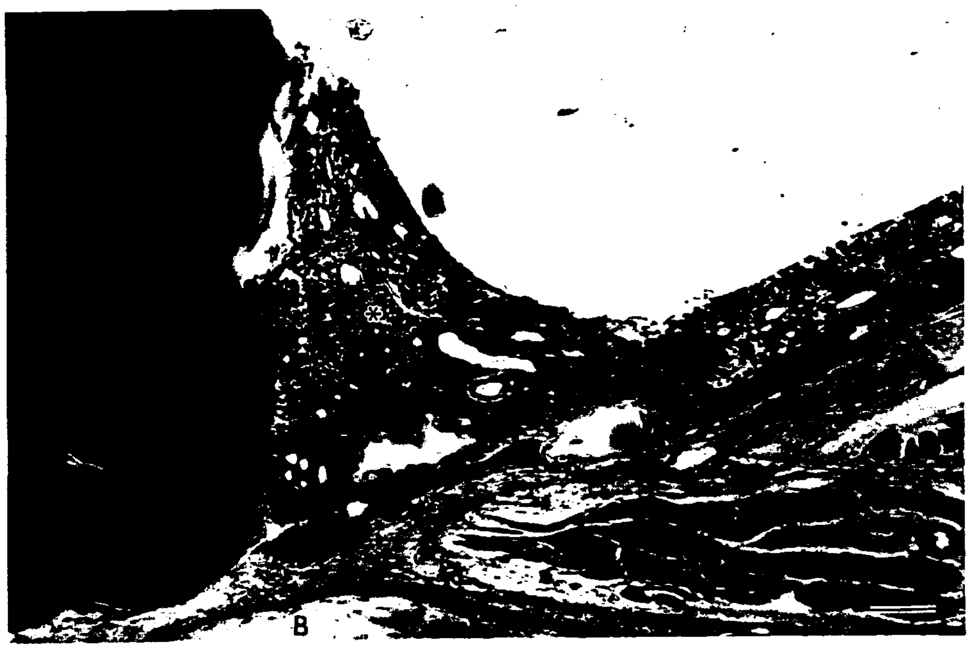

Fig. 3. TC-28. Higher magnification shows the opposite edge of the base pedestal shown in Fig. 2. Note the cluster of mixed inflammatory cells within the layers of subcutaneous tissue (*). Osseointegration is poor at the interface between the base pedestal and bone (B). Bar = 100 μm.

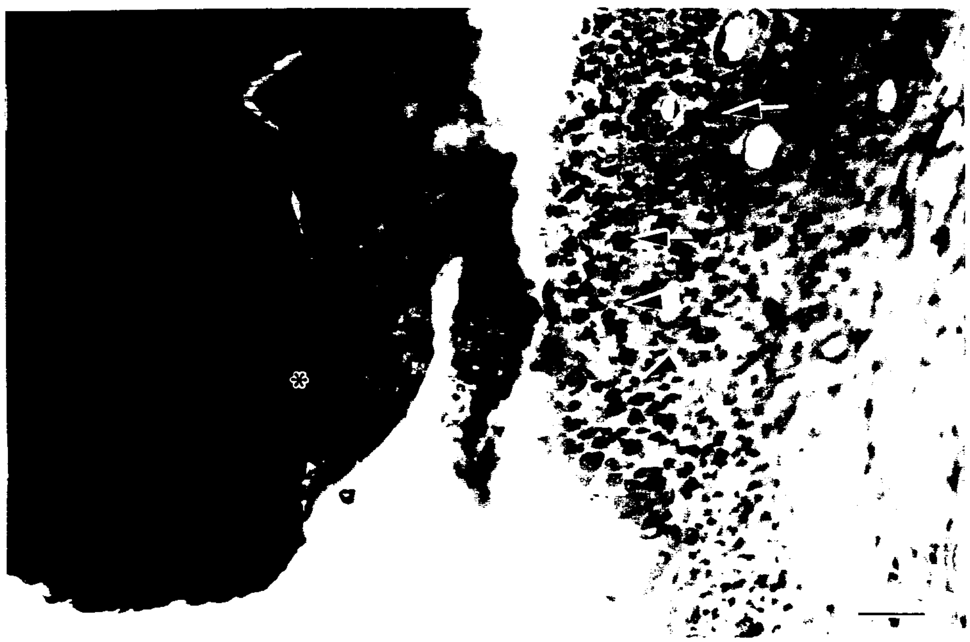

Fig. 4. TC-28. The edge of the base pedestal (*) is shown. Note the mixture of neutrophils (arrowheads) and larger mononuclear cells (arrows) adjacent to the base pedestal. The bone under the base pedestal is out of focus in this micrograph and is not visible. Bar = 200 μm.

Fig. 5. TC-28. The edge of the base pedestal is shown with a screw well inserted within the skull. Note the recessed area of the screw containing purulent material containing clotted fibrin material. (See also Fig. 6 for higher magnification of this area). Bar = 500 µm.

Fig. 6. TC-28. Higher magnification of the section in Fig. 5 shows the clotted fibrin material. Bar = 200 µm.

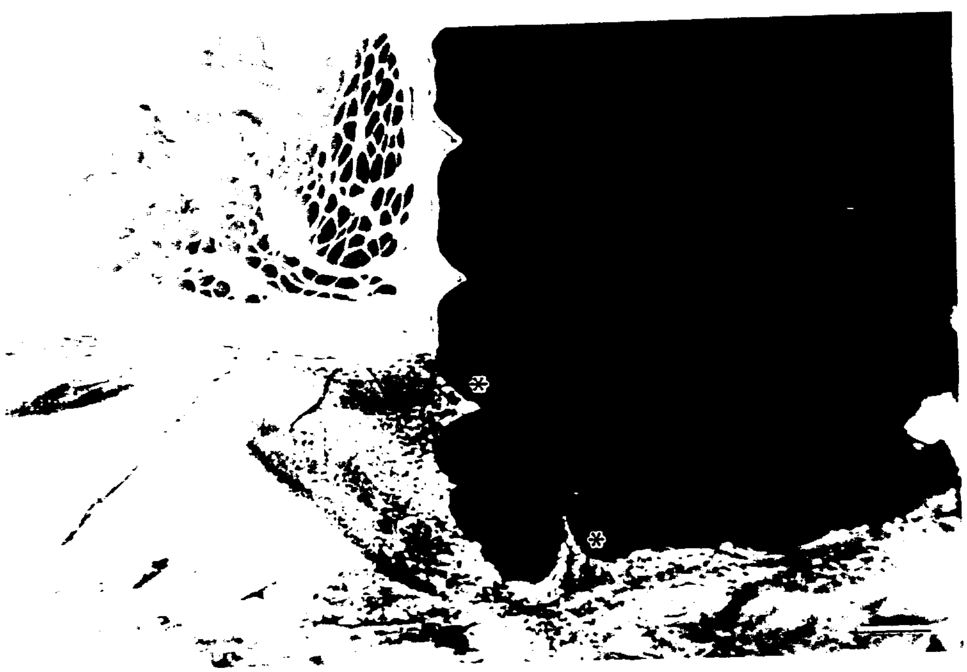

Fig. 7. TC-24. Higher magnification from Fig. 1 shows excellent osseointegration at the edge and bottom of the base pedestal (*). Bar = 200 µm.

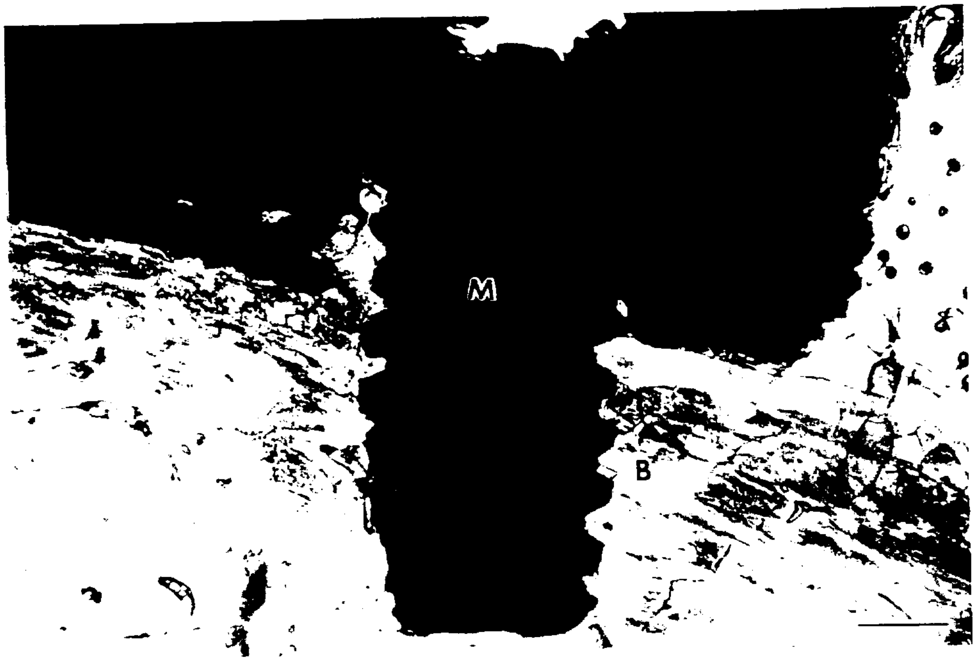

Fig. 8. TC-24. The interface between metal (M) and bone (B) of the base pedestal is shown. Note the presence of osteoid tissue within the deep groove of the screw. Bar = 500 µm.

DEVELOPMENT OF A HIGH DENSITY PERCUTANEOUS CONNECTOR SYSTEM

QUARTERLY REPORT #5
April 15, 1998 - July 15, 1998

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Abstract

This report summarizes activity over the period from April 15, 1998 through July 15, 1998 on NIH Contract N01-DC-7-2103, "Development of a High Density Percutaneous Connector System". A coordination meeting was held at HMRI on June 1st. Two implants were completed with the HMRI report in Appendix I. They showed good osseointegration with good skin attachment to Ti grooves in one and the beginnings of good skin attachment to Ti beads in the other. In the second, skin attachment was lost as a result of infection. Five implants are being prepared: a full electrostimulation, two with ribbon cables and beaded surfaces for skin attachment and two rings are at UWEB for Laminin-5 coating, also with ribbon cables. The Quick Disconnect design is nearing final stage and an 81-pin connector has been built with some success. Four sets of dummy connectors with CABAL-12 frit have been received. They show a shrinkage problem that is being resolved. The search for polymers to be used as a pin matrix continues.

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I. Background and Review of Contract Requirements

This report summarizes activity during the specified quarter, on NIH Contract N01-DC-7-2103, "Development of a High Density Percutaneous Connector System". Over the course of this contract, a high density, planar, low profile connector system is being developed that incorporates pad grid array technology. This technology has unique advantages as applied to a percutaneous interconnect system. In particular the connector system will be low in profile, easy to clean, sealed against ingress of contaminants, offer low mechanical resistance to mating and demating and provide a very high number of contacts in a small diameter. The connector system will be implanted in a suitable animal model and the appropriate electrical, mechanical, and biocompatible properties of the system will be assessed. The specific technical requirements of this connector system as detailed in the contract are explained below:

- The connector will incorporate a pedestal that can be attached to the skull in a mechanically stable manner. The pedestal will be designed to accept a replaceable connector assembly. All materials of the pedestal in contact with tissue will be biocompatible and the profile of the pedestal will be low enough to minimize any physical trauma during mating and demating of the connector or due to normal physical activities.

- The connector assembly will be high-density with at least 70 contacts. The electrical isolation between the contacts or between the contacts and the body should withstand at least 18 volts without breakdown. The connector contacts when mated should be capable of passing up to 20 mA of current with less than a 1.0 volt drop across the connection. A simple method of mating and demating the upper and lower surfaces of the connector should be provided. In addition, a convenient means to attach electrical leads to the connector is needed.

- The connector will be designed from materials that are durable and can withstand the physical abuse from normal activities of daily living. The interface between the connector and the skin must be such that the passage of microorganisms into the body and fluid drainage out of the body is prevented.

- In earlier studies connectors had 5 separate loops of insulated wire, each 2 inches long. Because of wire breakage observed during these studies it is necessary to make a more durable and a more realistic part. The present cable has a ribbon "cable" 1 inch long with five Pt/Ir wires, each 2 mils in diameter, coated with Parylene and Silicone. The wires are each formed into a loop so there are five loops for testing. The 2 mil wires are more rugged and easier to work with for initial tests, but 1 mil wires will be used after the ribbon cable concept is developed. An 18 volt bias will be maintained on the connector contacts and insulated wires relative to an implanted platinum wire connected to one of the unused contacts or the Ti connector body. The leakage current of the cable wires will be monitored and if more than 10 nanoamperes of current is detected, the source of the leakage will be identified and corrected.

- Performance of the connector system will be tested in a suitable animal model. After three to six months of implantation, the connector assembly will be explanted and gross and microscopic examinations will be performed to study the attachment of the pedestal to the skull, the attachment of the skin and soft tissue surrounding the pedestal to the pedestal wall and the reaction of adjacent tissue to the implanted device.

- Finally, design changes and improvements, if needed, will be recommended. A set of connectors will be fabricated and sent to the NIH for implantation. Initial testing will be in cats with final tests conducted in non-human primates.

II. Coordination Meeting

A coordination meeting was held at HMRI on June 1st. In attendance were Dr. Dave Edell, Dr. Bill Agnew, Dr. Doug McCreery, Dr. Al Lossinsky, Dr. Ted Yuen, Mr. Leo Bullara, and Dr. Lou Rucker.

The histology from experiments during the prior six months were reviewed and discussed by Dr. Lossinsky. Pockets that could be infection sites were pointed out with the recommendation that connector design and surgical procedures be modified where possible to prevent or reduce such pockets. Good osseointegration was observed. Skin health and attachment varied depending on the experiment. Smooth surfaces showed little or no attachment and infection.

Skin growth and attachment was identified as a significant topic that requires extensive work. Methods to promote the desired skin growth were discussed including grooved Ti, Ti beads, electrostimulation and Laminin-5. It is not within the scope of this study to explore each exhaustively so the objective will be to start with the known "standard", grooved Ti, and to make significant incremental improvements.

The recent failure of the first ribbon cable was discussed with the conclusion that the placement needs to be changed. Future ribbon implants will keep the cable away from sources of movement such as the Temporalis muscle and ears to the extent possible. A midline implant will be attempted.

Combination implants have been attempted recently in which a control surface, such as grooved Ti, and test surface were on opposite sides of the same implant. In some cases one surface had trouble leading to infection and loss of most of the experiment. Dr. Agnew recommended that split experiments be avoided in the future. If it is desirable to implant two surfaces in the same animal a double implant should be considered. It was felt that the space between the implants would isolate problems at one site from the other site. The use of a "T" or "S" incision for various double implants was discussed.

Screw strength is a concern; two cases were recently reported of failure of the hex portion of the screw head at 14 oz-inches torque. These are commercially pure grade 2 Titanium. In the future the Ti-6Al-4V alloy will be used for added strength. The connector body material will not change.

The initial results of work by IJ Research to use a ceramic frit as a pin matrix were reported. Shrinkage seems to be a problem. The search for alternative materials (polymers) for use as a long-term pin matrix was reported by Dr. Rucker. A hot box for accelerated life testing is being constructed at BioElectric Corporation.

The accelerated implant schedule to start during June was discussed with the list of implants including electrostimulation, Ti bead surface, Laminin-5 surface, cable experiments and at least one 81-pin connector. Future experiments will possibly be desirable combinations such as grooved Ti or Ti beads with Laminin-5 and/or electrostimulation.

It was proposed that meetings be held every six months instead of annually and that a frequent "newsletter" be emailed to each participant. Conference calls will be used as needed to keep the team in touch. The next coordination meeting is expected in December.

III. HMRI Work

Two implants were completed during the quarter. The first was a dummy for study of skin attachment to two surfaces: smooth and Ti beaded. The second was a half-electrostimulation experiment. The HMRI report is contained in Appendix I.

The results generally showed good osseointegration and skin integration except to the smooth Ti surface. This was originally intended to be a grooved Ti surface, but the surface was lost during the bead sintering. The implant proceeded despite the surface loss with the result that the Ti beaded surface showed very good skin attachment until infection from the smooth side spread to the beads. With infection from the smooth implant last fall and from this implant, there will be no more smooth surfaces implanted. With the apparent success of the Ti bead surface two full Ti bead surfaces will be implanted this summer for comparison to other grooved Ti surfaces.

The half Ti bead experiment also had the first ribbon cable. Initial results reported last quarter showed good performance with low leakage. However, the ribbon was placed under the Temporalis muscle. The ribbon moved to a position over the muscle, apparently because of scalp movement and/or head bumping. Three of the five loops opened at the exit from the connector body because of the sharp upward "kink" in the cable caused by the movement to a higher position. In future studies the cable will be positioned differently. The maximum leakage on all loops ranged from 2.8 to 3.8 nA; the required limit is 10 nA.

The half-electrostimulation implant showed good skin adhesion, but the skin dropped down to the level of the pedestal. The reasons for the drop are that this was a midline implant (the first) where the skin is thinner and the animal was a small female. Future work will use medium size or larger males. In this experiment the skin attached successfully to the pedestal with 4 mil deep grooves on a 5 mil pitch. Note that this is a much deeper groove than other studies indicate would be successful for skin attachment or to prevent epithelial downgrowth. The initial skin attachment to the finer grooved surface intended for that purpose was apparently successful, but the desired comparison between the electrostimulated and unstimulated sides was lost. There is no intent to repeat the experiment; future electrostimulation implants will be full stimulation over the entire connector surface.

IV. Change of Cable Geometry

Last quarter a new geometry for the ribbon cable was reported. That configuration was tested as described in the HMRI section and will continue to be used with one exception: for initial tests a two mil Pt/Ir wire instead of one mil will be used. The reason is that the two mil wire is easier to work with and is more rugged when implanted. The one mil wire will be tested at a later date.

V. Status of Fritting Experiment

Four sets of CABAL-12 and TA-23 ceramic frit experiments have been received from IJ Research. The TA-23 showed significant problems with excessive voids and failure to seal to the metal pins and connector body. These problems could probably be solved, but the CABAL-12 looked satisfactory except for what Dr. Rick Yoon (President of IJR and technical consultant in this work) calls shrinkage. As work progressed there seemed to be less shrinkage, but ten new dummy connectors to be delivered for fritting in August are being prepared 150 mils thick instead of 120 mils, the standard connector thickness. With the extra thickness these parts can be ground to 120 mils eliminating gaps resulting from shrinkage.

The fabrication of preforms has become more reliable. A delay of approximately six months in this work was caused by breakage of pins in the preform mold. These pins make the holes into which our Pt/Ir connector pins are inserted prior to firing the ceramic.

Cracking of the frit from differing thermal coefficients of expansion was expected at least occasionally. None have been observed in any work for both CABAL-12 and TA-23 and for three pin materials, Pt/Ir, Mo and Ta. This is a significant positive step in use of the ceramic materials.

Later in this report it is indicated that an 81-pin connector has been made using 14 mil diameter pins. Dr. Yoon has expressed doubt that a preform can be made for this size pin so alternatives must be found.

VI. Investigation Into Other Pin Matrix Materials

The hot box for test of alternative pin materials was completed in June and found to operate reliably at 100 °C. Since aging tests will be carried out at 80 to 90 °C this is considered adequate. There may be some changes in the insulating material being used in the future.

The Ti fixtures containing various test materials in the last QPR have not been completed because some materials have not yet become available. Completion is expected in August at which time testing will start.

VII. Connection of Top and Bottom Sections with a "Quick Disconnect" Mechanism

The design of a new Quick Disconnect mechanism is near completion with plans to fabricate two or three units in August. The basic design is similar to the existing design, but with an external 1/32 screw thread added to the top of the lower connector body. This protrudes above the ring into which the lower connector is inserted. The top connector has a mating internal screw thread on a floating ring with a knurled outside surface for finger grip. There are two offset protrusions in the lower connector with mating holes in the top connector for alignment. The overall diameter of the mechanism is slightly larger than the 0.530" diameter of the older design and the height is slightly greater even though the top cap and cable have been redesigned to reduce the height.

Other alternatives have been and are being considered, but not actively pursued at this time. Concerns are overall height, ease of installation by the patient, ease of installation by a surgeon, reliability, potential for increasing pin number in the future and appearance.

VIII. Reliability of the Anisotropic Material from Shin-Etsu

The new GMB material from Shin-Etsu was used successfully in one implant (tc28) at HMRI. The GMB material is 0.3 mm thick, 0.1 mm (4 mils) thicker than the connector design called for. However, this created no problem. Each screw turn moves 12 mils and the design is for four threads to engage. The additional thickness of the GBM material decreases the thread engagement by 1/3 of a turn which can be compensated with a longer screw in the future.

As reported in the last QPR, the new material allows use of smaller diameter pins, which is reported in section VII below.

IX. 81-Pin Connector Prototype

The GBM elastomer allows use of pin diameters down to 14 mils. The present design uses 17. New alumina inserts were ordered to fit in the existing connector body with a 9x9 pin array instead of the existing 8x8 pin array. This increases the pin count to 81. Initial test was with Copper wire to reduce costs and it was found that the wire was not held straight during fabrication so the pins between the upper and lower connector were not reliable. To correct this a new connector with four instead of two alumina inserts is being constructed. This should hold the pins in alignment. The alumina protrudes slightly above the connector surfaces and is ground flat as a normal part of the fabrication process.

Using the four inserts also provides the possibility of having a solid ceramic core without firing the ceramic in the connector as is being done at IJR. A small amount of medical grade epoxy or Silicone can be used to hold the ceramic in place. Dr. Edell has been asked to look into the possibility of this configuration being a ten-year pin-matrix material.

X. Skin Growth

Two connectors have been built with Ti beaded surfaces and five loop cables. We are waiting for completion of new pedestals with beads before shipping these parts

Two rings were sent to the University of Washington Biomedical Engineering group at the University of Washington during May for treatment with Laminin-5 to encourage skin attachment at the epidermal level. The Laminin-5 is being placed on top of the normal grooved Ti surface to prevent epithelial downgrowth. The rings are expected back by the end of July.

XI. Activities for the Sixth Quarter

During the next quarter:

- Implant the full electrostimulation experiment.
- Implant two connectors with Ti beads to study skin growth.
- Implant two connectors with Laminin-5 to study skin growth.
- Implant four cables on the Ti bead and Laminin-5 connectors.
- Continue work on the ceramic frit with IJ Research.
- Continue to look for long-term pin matrix materials using accelerated aging.
- Start Parylene-Silicone interface accelerated life testing.
- First tests of the Quick Disconnect connector.
- Make and test the 81-pin connector design - implant if possible.

Appendix I

HMRI Report